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(54) Title: SUGAR-SUBSTITUTED 2-AZETIDINONES USEFUL AS HYPOCHOLESTEROLEMIC A GENTS

(57) Abstract

Hypocholesterolemic sugar-substituted 2-azetidinones are dislcosed, as well as a method of lowering cholesterol by administering said compounds, pharmaceutical compositions containing them, and the combination of a sugar-substituted 2-azetidinone cholesterol-lowering agent and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis.

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SUGAR-SUBSTITUTED 2-AZETIDINONES USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to sugar-substituted 2-azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a sugar-substituted 2-azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis.

Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. In addition to regulation of dietary cholesterol, the regulation of whole-body cholesterol homeostasis in humans and animals involves modulation of cholesterol biosynthesis, bile acid biosynthesis, and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and, for this reason, it is a prime determinant of plasma cholest rol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently m tabolized to low density lipoproteins

(LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When cholesterol absorption in the intestines is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is a decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of an inhibition of intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

Several 2-azetidinone compounds have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls: WO 93/02048 describes 2-azetidinone compounds wherein the 3-position substituent is arylalkylene, arylalkenylene or arylalkylene wherein the alkylene, alkenylene or alkyleneportion is interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes 2-azetidinone compounds wherein the 3-position substituent is an arylalkylspirocyclic group; WO 95/08532 describes 2-azetidinone compounds wherein the 3-position substituent is an arylalkylene group substituted in the alkylene portion by a hydroxy group; PCT/US95/03196, filed March 22, 1995, describes compounds wherein the 3-position substituent is an aryl(oxo or thio)alkylene group substituted in the alkylene portion by a hydroxy group; and U.S. Serial No. 08/463,619, filed June 5, 1995, describes the preparation of compounds wherein the 3-position substituent is an arylalkylene group substituted in the alkylene portion by a hydroxy group, and wherein the alkylene group is attached the the azetidinone ring by a -$S(O)_{0-2}$- group. The cited patent applications are incorporated herein by reference.

Also, European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease stat s, .g. atherosclerosis.

Other known hypochol st rolemics include plant extracts such as sapogenins, in particular tigogenin and diosgenin. Glycoside

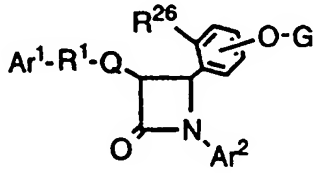
derivatives of tigogenin and/or diosgenin are disclosed in PCT International publications WO 94/00480 and WO 95/18143.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, *80*, 5 (1989), p. 1101-1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs* , *36* (Suppl. 3) (1988), p. 63-71).

SUMMARY OF THE INVENTION

The present invention relates to sugar-substituted 2-azetidinones, especially to glucose-derived conjugates of cholesterol-lowering 2-azetidinones having an aryl or substituted aryl group as a substituent at the 1-position and having a hydroxy-substituted phenyl group, especially a 4-hydroxyphenyl group, at the 4-position.

Compounds of the present invention are represented by the formula I

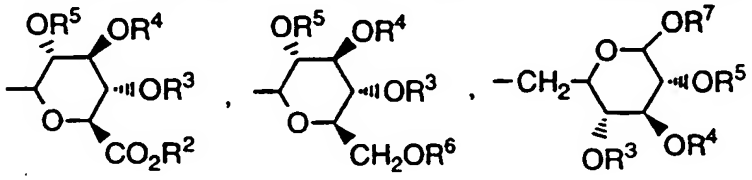


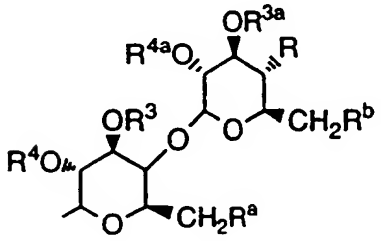
I

or a pharmaceutically acceptable salt thereof, wherein

R^{26} is H or OG^1;

G and G^1 are independently selected from the group consisting of H,





and

provided that when R^{26} is H or

OH, G is not H;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy or -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl and -C(O)aryl;

R^{30} is independently selected form the group consisting of R^{32}-substituted T, R^{32}-substituted-T-(C_1-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C7)cycloalkyl and R^{32}-substituted-(C_3-C7)cycloalkyl(C_1-C_6)alkyl;

R^{31} is independently selected from the group consisting of H and (C_1-C_4)alkyl;

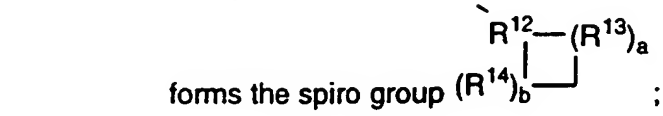
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C_1-C_4)alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, (C_1-C_4)alkoxy, methylenedioxy, oxo, (C_1-C_4)alkylsulfanyl, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH(C_1-C_4)alkyl, -C(O)-N((C_1-C_4)alkyl)$_2$, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar^1 is aryl or R^{10}-substituted aryl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone,



forms the spiro group ; and

R^1 is selected from the group consisting of

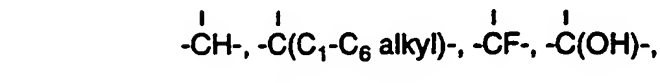
$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e-E-(CH_2)_r-$, wherein E is -O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2-C_6)$alkenylene-; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

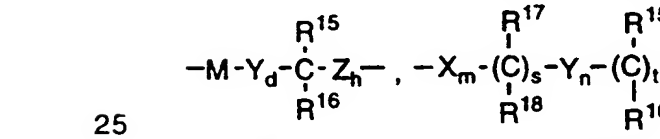
R^{12} is



R^{13} and R^{14} are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C($di-(C_1-C_6) alkyl), -CH=CH- and $-C(C_1-C_6$ alkyl)=CH-; or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when R^{14} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

and when Q is a bond, R^1 also can be:



M is -O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)$alkyl- and $-C($di-(C_1-C_6)alkyl);

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group

consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1\text{-}5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $S(O)_{0\text{-}2}R^{21}$, $-O(CH_2)_{1\text{-}10}\text{-}COOR^{19}$, $-O(CH_2)_{1\text{-}10}CONR^{19}R^{20}$, $-(C_1\text{-}C_6$ alkylene)-$COOR^{19}$, $-CH{=}CH\text{-}COOR^{19}$, $-CF_3$, $-CN$, $-NO_2$ and halogen;

R^{15} and R^{17} are independently selected from the group consisting of $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$ and $-O(CO)NR^{19}R^{20}$; R^{16} and R^{18} are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl and aryl; or R^{15} and R^{16} together are =O, or R^{17} and R^{18} together are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

and when Q is a bond and R^1 is $-X_j\text{-}\underset{\displaystyle R^{16}}{\overset{\displaystyle R^{15}}{(C)_v}}\text{-}Y_k\text{-}S(O)_{0\text{-}2}-$, Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

R^{21} is $(C_1\text{-}C_6)$alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, $(C_1\text{-}C_6)$alkyl, aryl $(C_1\text{-}C_6)$alkyl, $-C(O)R^{19}$ or $-COOR^{19}$;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, -COOH, NO_2, $-NR^{19}R^{20}$, -OH and halogeno; and

R^{25} is H, -OH or $(C_1\text{-}C_6)$alkoxy.

Ar^2 is preferably phenyl or R^{11}-phenyl, especially (4-R^{11})-substituted phenyl. Preferred definitions of R^{11} are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

Ar^1 is preferably phenyl or R^{10}-substituted phenyl, especially (4-R^{10})-substituted phenyl. A preferred definition of R^{10} is halogeno, especially fluoro.

There are several preferred definitions for the -R^1-Q- combination of variables:

Q is a bond and R^1 is lower alkylene, preferably propylene;

Q is a spiro group as defined above, wherein preferably R^{13} and R^{14} are each ethylene and R^{12} is -CH- or -C(OH)- , and $R^1$is $-(CH_2)_q$ wherein q is 0-6;

Q is a bond and R^1 is $-M-Y_d-\underset{\displaystyle R^{16}}{\overset{\displaystyle R^{15}}{C}}-Z_h-$ wherein the variables are chosen such that R^1 is -O-CH_2-CH(OH)-;

Q is a bond and R^1 is $-X_m-\underset{\displaystyle R^{18}}{\overset{\displaystyle R^{17}}{(C)_s}}-Y_n-\underset{\displaystyle R^{16}}{\overset{\displaystyle R^{15}}{(C)_t}}-Z_p-$ wherein the variables are chosen such that R^1 is -CH(OH)-$(CH_2)_2$-; and

Q is a bond and R^1 is $-X_j-\underset{\displaystyle R^{16}}{\overset{\displaystyle R^{15}}{(C)_v}}-Y_k-S(O)_{0-2}-$ wherein the variables are chosen such that R^1 is -CH(OH)-CH_2-$S(O)_{0-2}$-.

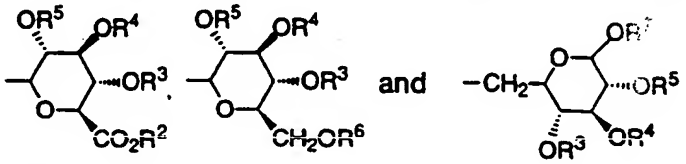
A preferred compound of formula I, therefore, is one wherein G and G^1 are as defined above and in which the remaining variables have the following definitions:

Ar^1 is phenyl or R^{10}-substituted phenyl, wherein R^{10} is halogeno;

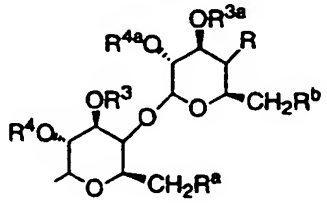
Ar^2 is phenyl or R^{11}-phenyl, wherein R^{11} is 1 to 3 substituents independently selected from the group consisting of C_1-C_6 alkoxy and halogeno;

Q is a bond and R^1 is lower alkylene; Q, with the 3-position

ring carbon of the azetidinone, forms the group  wherein preferably R^{13} and R^{14} are each ethylene and a and b are each 1, and wherein R^{12} is -CH- or -C(OH)- ; Q is a bond and R^1 is $-O-CH_2-CH(OH)-$; Q is a bond and R^1 is $-CH(OH)-(CH_2)_{2}-$; or Q is a bond and R^1 is $-CH(OH)-CH_2-S(O)_{0-2}-$.

Preferred variables for G and G^1 groups of the formula  are as follows:

R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl.

Preferred variables for group G or G^1 of the formula  are as follows:

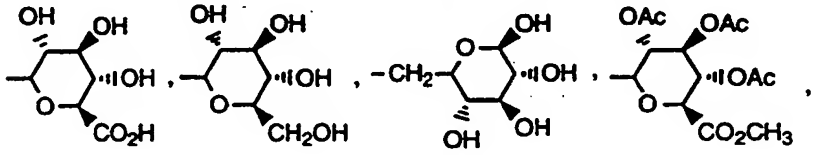
R^3, R^{3a}, R^4 and R^{4a} are selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl;

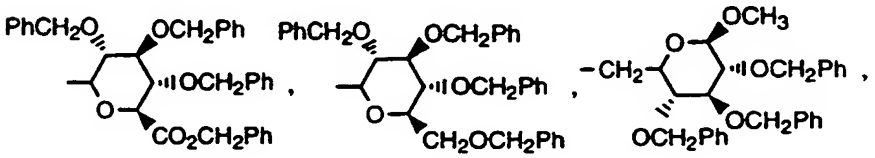
R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy and $-W-R^{30}$, wherein W is -O-C(O)- or $-O-C(O)-NR^{31}-$, R^{31} is H and R^{30} is (C_1-C_6)alkyl, $-C(O)-(C_1-C_4)$alkoxy-(C_1-C_6)alkyl, T , T-(C_1-C_6)alkyl, or T or T-(C_1-C_6)alkyl wherein T is substituted by one or two halogeno or (C_1-C_6)alkyl groups.

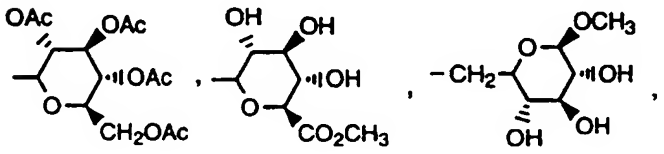
Preferred R^{30} substituents are 2-fluorophenyl, 2,4-difluorophenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxycarbonyl thyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxycarbonylbutyl and phenyl. Pref rred combinations of R, R^a and R^b are as follows: 1) R, R^a and R^b are independently -OH or $-O-C(O)-NH-R^{30}$, especially wherein

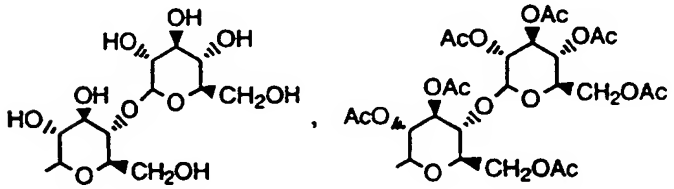
R^a is -OH and R and R^b are -O-C(O)-NH-R^{30} and R^{30} is selected from the preferred substituents identified above, or wherein R and R^a are -OH and R^b is-O-C(O)-NH-R^{30} wherein R^{30} is 2-fluorophenyl, 2,4-difluorophenyl, 2,6-dichlorophenyl; 2) R^a is -OH, halogeno, azido or (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, R^b is H, halogeno, azido or (C_1-C_6)alkoxy(C_1-C_6)-alkoxy, and R is -O-C(O)-NH-R^{30}, especially compounds wherein R^a is -OH, R^b is H and R^{30} is 2-fluorophenyl; 3) R, R^a and R^b are independently -OH or -O-C(O)-R^{30} and R^{30} is (C_1-C_6)alkyl, T , or T substituted by one or two halogeno or (C_1-C_6)alkyl groups, especially compounds wherein R is -OH and R^a and R^b are -O-C(O)-R^{30} wherein R^{30} is 2-furyl; and 4) R, R^a and R^b are independently -OH or halogeno. Three additional classes of preferred are compounds are those wherein the $C^{1'}$ anomeric oxy is beta, wherein the $C^{2'}$ anomeric oxy is beta, and wherein the R group is alpha.

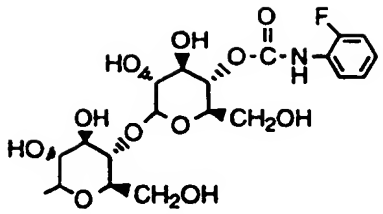
G and G^1 are preferably selected from:









and 

wherein Ac is acetyl and Ph is phenyl. Preferably, R^{26} is H or OH, more preferably H. The -O-G substituent is preferably in the 4-position of the phenyl ring to which it is attached.

This invention also relates to the use of a sugar-substituted 2-azetidinone, especially one of formula I, as a hypocholesterolemic agent in a mammal in need of such treatment.

In another aspect, the invention relates to a pharmaceutical composition comprising a sugar-substituted 2-azetidinone, especially one of formula I, in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing hepatic cholesterol ester levels, a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sugar-substituted 2-azetidinone of this invention, especially one of formula I, and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a sugar-substituted 2-azetidinone for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a sugar-substituted 2-azetidinone) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a sugar-substituted 2-azetidinone, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a sugar-substituted 2-azetidinone in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynth sis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION:

As used herein, the term "alkyl" or "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms and "alkoxy" similarly refers to alkoxy groups having 1 to 6 carbon atoms.

"Alkenyl" means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated. Similarly, "alkynyl" means straight or branched carbon chains having one or more triple bonds in the chain. Where an alkyl, alkenyl or alkynyl chain joins two other variables and is therefore bivalent, the terms alkylene, alkenylene and alkynylene are used.

"Cycloalkyl" means a saturated carbon ring of 3 to 6 carbon atoms, while "cycloalkylene" refers to a corresponding bivalent ring, wherein the points of attachment to other groups include all positional isomers.

"Halogeno" refers to fluorine, chlorine, bromine or iodine radicals.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl. "Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution. R^{24}-benzyl and R^{24}-benzyloxy refer to benzyl and benzyloxy radicals which are substituted on the phenyl ring.

The above statements, wherein, for example, R^{19}, R^{20} and R^{25} are said to be independently selected from a group of substituents, means that R^{19}, R^{20} and R^{25} are independently selected, but also that where an R^{19}, R^{20} or R^{25} variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R^{10} is $-OR^{19}$ wherein R^{19} is hydrogen, R^{11} can be $-OR^{19}$ wherein R^{19} is lower alkyl). Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents which can be present.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, eith r by r acting optically pure or

optically enriched starting materials or by separating isomers of a compound of formula I.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than other isomers.

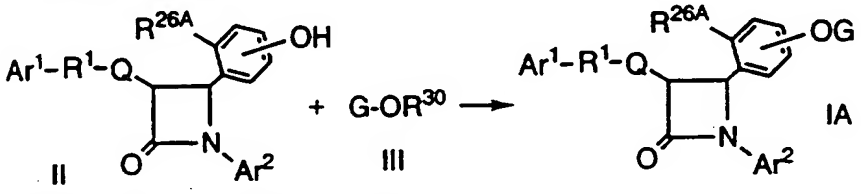
Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

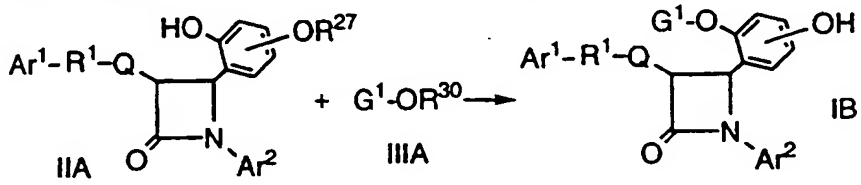
Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]b nz ne-methanamine hydrochloride). Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin, fluvastatin and simvastatin.

The cholesterol-lowering 2-azetidinone portions of the compounds of formula I can be prepared by known methods, for example WO 93/02048 describes the preparation of compounds wherein -R^1-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532 describes the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein -R^1-Q- is a hydroxy-substituted alkylene attached to the Ar^1 moiety through an -O- or $S(O)_{0-2}$- group; and U.S. Serial No. 08/463,619, filed June 5, 1995, describes the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group attached the the azetidinone ring by a -$S(O)_{0-2}$- group.

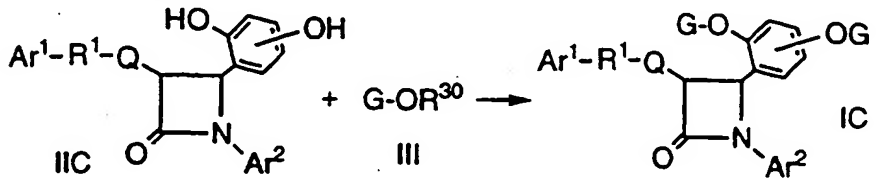
Compounds of the present invention are generally prepared by reacting a 4-(hydroxy- or dihydroxy)-phenyl-2-azetidinone with a sugar derivative. For example, an azetidinone of formula II, wherein R^{26A} is H or OH, is reacted with one equivalent of a sugar derivative of formula III:



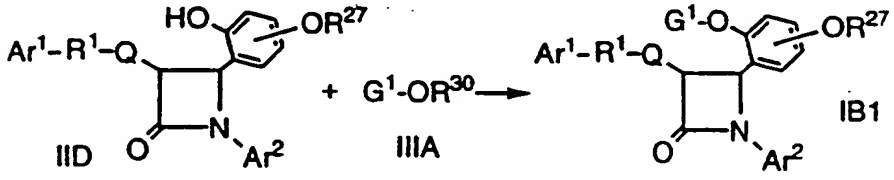
wherein R^{30} is hydrogen or -$CNHCCl_3$ and the remaining variables are as defined above to obtain a compound of formula IA, wherein R^{26A} is H or OH. To prepare a compound of formula IB, wherein R^{26} is OG^1, wherein G^1 is not H, and G is H, an azetidinone of formula IIA, wherein R^{26} is OH and R^{27} is a suitable hydroxy protecting group, is reacted with a sugar derivative of formula IIIA, wherein R^{30} is as defined above, followed by removal of the R^{27} protecting group:

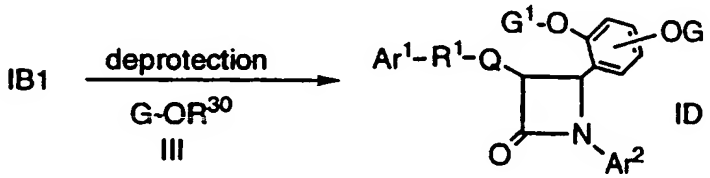


To prepare a compound of formula IC, wherein both G^1 and G are the same, but are not H, a dihydroxy compound of formula IIC is reacted with an excess of $G\text{-}OR^{30}$:



To prepare compounds of formula ID wherein G and G^1 are both not H and are not the same sugar derivative, a compound of formula IA wherein R^{26A} is OH can be reacted with a sugar of the formula $G^1\text{-}OR^{30}$. Alternatively, one of the hydroxy substituents on the 4-position phenyl of a compound of formula IIC is protected prior to reaction with the sugar derivative to be attached to the unprotected hydroxy group, and after reaction with the first sugar derivative, the hydroxy-protecting group is removed and the second sugar derivative is reacted with the previously-protected hydroxy group. For example:



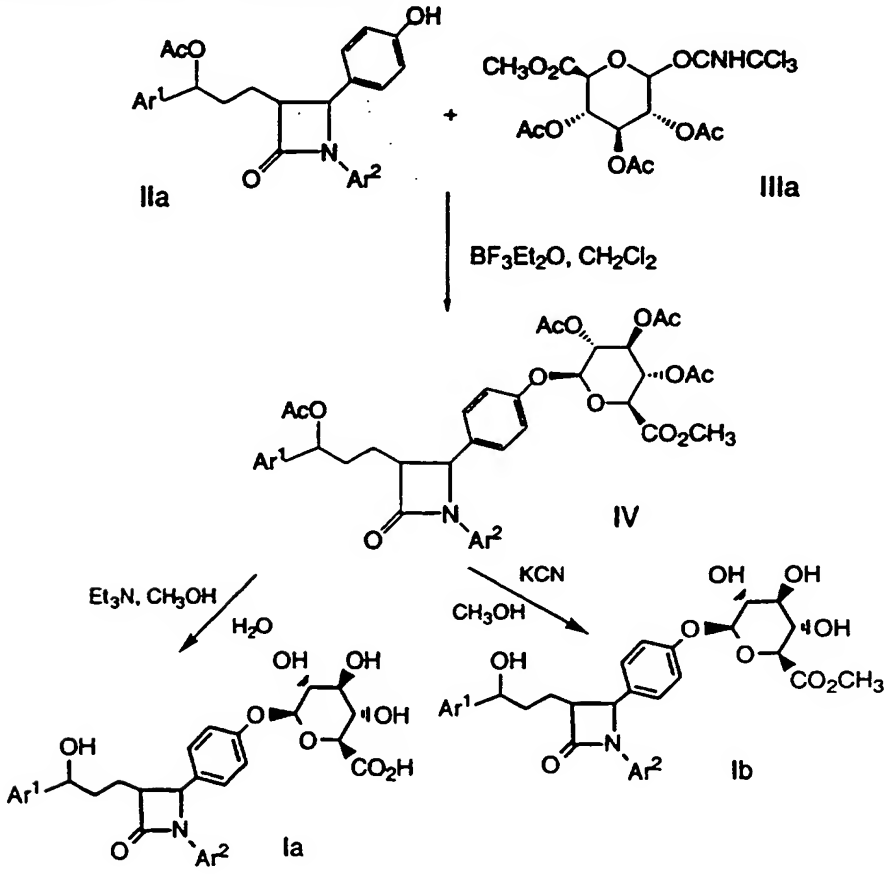


Sugars and the derivatives thereof as defined by $G\text{-}OR^{30}$ and $G^1\text{-}OR^{30}$ are known in the art or are readily prepared by known methods.

Preferably, the reactions described above involve a sugar derivative wherein the non-reactive hydroxy groups are protected by suitable protecting groups as defined above for R^2, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^7 other than hydrogen, preferably lower alkyl, acetyl or benzyl, which groups can be removed after the reaction to provide the sugar conjugate. When the 1- and 3-position side chains of the 2-azetidinone include substituent groups which are reactive under the conditions

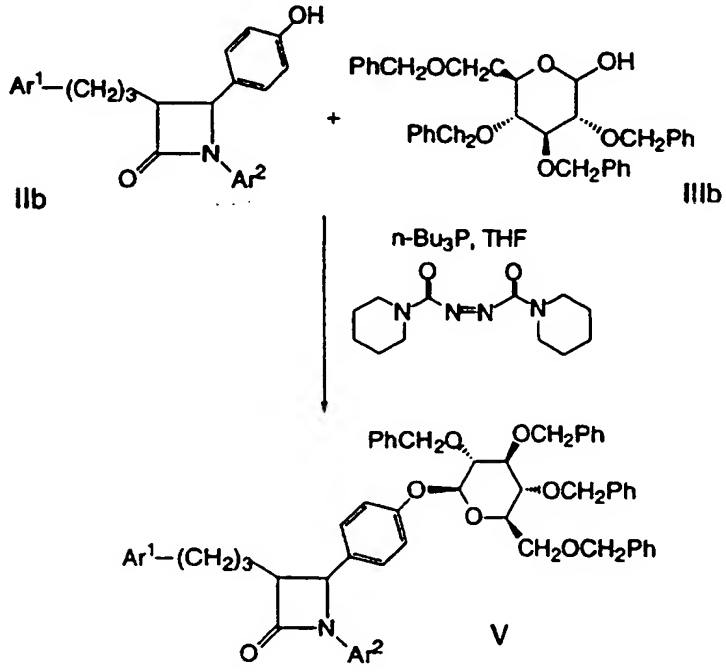
used, said reactive groups are protected by suitable protecting groups prior to reaction with the sugar or the derivative thereof, and the protecting groups are subsequently removed. Depending on the nature of the protecting groups, the protecting groups on the sugar portion and on the 1- and 3-position side chains of the azetidinone can be removed sequentially or simultaneously.

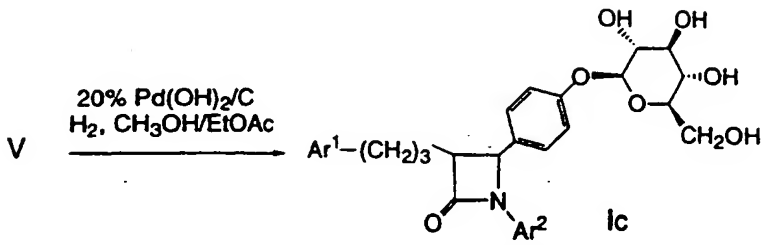
For example, compounds of formula I wherein Ar^1-R^1-Q- is Ar^1-CH(OH)-$(CH_2)_2$-, i.e. compounds of formula Ia and Ib, can be prepared according to the following reaction scheme, wherein an azetidinone of formula IIa is reacted with a sugar derivative of the formula G-OCNHCCl$_3$. The scheme is shown for a compound wherein R_{26} is H and a specific G-OCNHCCl$_3$ group is exemplified, but a similar procedure can be used to prepare compounds wherein R^{26} is -OG^1 and for other G-OCNHCCl$_3$ groups:



In the first step, the azetidinone of formula IIa is reacted with the sugar derivative of formula IIIa in the presence of a coupling agent such as BF_3 etherate in an inert solvent such as CH_2Cl_2. The reaction is carried out at temperatures of -20 to -25 °C for a period of about two hours. In the second step, either the sugar-substituted azetidinone of formula IV is treated with a base such as triethylamine in a solvent such as methanol and water to remove the acetyl and alkyl protecting groups to obtain a compound of formula Ia, or the sugar-substituted azetidinone of formula IV is treated with a reagent such as KCN in a solvent such as methanol to remove the acetyl protecting groups but leave the alkyl protecting group to obtain a compound of formula Ib. The compound of formula Ib can be further reduced by a reagent such as LiOH to obtain the compound of formula Ia.

Compounds of formula I wherein Ar^1-R^1-Q- is Ar^1-$(CH_2)_3$-, i.e. compounds of formula Ic, can be prepared according to the following reaction scheme, wherein an azetidinone of formula IIb is reacted with a sugar derivative of the formula G-OH. The scheme is shown for a compound wherein R^{26} is hydrogen and with a specific G-OH group, but a similar procedure can be used to prepare compounds wherein R^{26} is -OG^1 and for other G-OH groups:





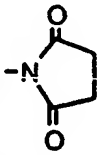
In the first step, the azetidinone of formula IIb is reacted with a sugar derivative of formula IIIb in an inert solvent such a tetrahydrofuran in the presence of n-tributylphosphine and 1,1'-(azodicarbonyl)dipiperidine. The resultant sugar-substituted azetidinone is reduced with a reagent such as $Pd(OH)_2/C$ in an alcoholic solvent under H_2 gas to remove the benzyl protecting groups to obtain a compound of formula I.

Starting materials of formula IIb are known. Compounds of formula IIa can be prepared from the corresponding (3-hydroxy-3 Ar^1-propyl)-2-azetidinone by treatment with acetic anhydride and dimethylaminopyridine (DMAP) in an inert solvent such as CH_2Cl_2 to obtain the corresponding di-acetyl compound, followed by treatment with guanidine to obtain the 4-hydroxyphenyl compound. Starting materials of formula II wherein Ar^1-R^1-Q- is as defined above for formula I can be prepared by similar methods or others well known in the art.

Starting materials of formula IIIb are known in the art or prepared by well known methods. Compounds of formula IIIa are prepared by treating the corresponding compound of formula IIIb with trichloroacetonitrile in an inert solvent such as CH_2Cl_2 in the presence of Cs_2CO_3.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

Table 1

Group to be Protected	Group to be Protected and Protecting Group
−COOH	−COOalkyl, −COObenzyl,−COOphenyl
>NH	>NCOalkyl, >NCObenzyl, >NCOphenyl; >$NCH_2OCH_2CH_2Si(CH_3)_3$, >$NC(O)OC(CH_3)_3$, >N-benzyl, >$NSi(CH_3)_3$, >$NSi\text{-}C(CH_3)_3$ (CH_3 / CH_3)
$=NH_2$	
−OH	$-OCH_3$, $-OCH_2OCH_3$, $-OSi(CH_3)_3$, $-OSi\text{-}C(CH_3)_3$ (CH_3 / CH_3); or $-OCH_2$phenyl

We have found that the compounds of this invention lower plasma lipid levels and hepatic cholesterol ester levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the esterification and/or intestinal absorption of cholesterol; they are therefore useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

Compared to the 2-azetidinone cholesterol lowering agents which are not sugar-substituted, the compounds of this invention have several pharmacological and physical advantages. The compounds are absorbed at a slower rate, give lower plasma levels and higher intestinal levels. Previous testing indicated the intestine as the likely site of activity of the 2-azetidinone compounds lacking a sugar substituent. See E. J. Sybertz et al, "SCH 48461, a Novel Inhibitor of Cholesterol Absorption," *Atherosclerosis X*, d. F.P. Woodward et al (Elsevier, 1995), pp. 311-315; and B.G. Salisbury et al,

"Hypercholesterolemic Activity of a Novel Inhibitor of Cholesterol Absorption," *Atherosclerosis* , 115 (1995), pp. 45-63. The instantly claimed compounds, which are excreted in the bile, provide efficient delivery of the compound to the desired site while minimizing systemic exposure, thereby decreasing potential toxicity problems.

In addition to the compound aspect, the present invention also relates to a method of lowering plasma cholesterol levels, which method comprises administering to a mammal in need of such treatment a hypocholesterolemic effective amount of a compound of formula I of this invention. The compound is preferably administered in a pharmaceutically acceptable carrier suitable for oral administration.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I of this invention and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional oral dosage form such as capsules, tablets, powders, cachets, suspensions or solutions. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesterolemic dose of a compound of formula I is about 0.001 to about 30 mg/kg of body weight per day, preferably about 0.001 to about 1 mg/kg. For an average body weight of 70kg, the dosage level is therefore from about 0.1 to about 100 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For the combinations of this invention wherein the substituted azetidinone is administered in combination with a cholesterol biosynth sis inhibitor, the typical daily dose of the chol sterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divid d dosages, usually once or twice a day: for example, for HMG CoA reductase inhibitors, about 10

to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2 g per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a sugar-substituted 2-azetidinone absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis and trans refer to the relative orientations at the ß-lactam 3- and 4-positions.

Preparation A

1-(4-Fluorophenyl)-3(R)-[3(S)-acetyloxy-3-(4-fluorophenyl)-propyl)]-4(S)-(4-hydroxyoxyphenyl)-2-azetidinone

Step 1: 1-(4-Fluorophenyl-3(R)-[3(S)-acetyloxy-3-(4-fluorophenyl)-propyl)]-4(S)-(4-ac tyloxyphenyl)-2-azetidinone

Add acetic anhydride (1.03 mL, 10.96 mmol) to a room temp rature solution of 1-(4-fluorophenyl-3(R)-[3(S)-hydroxy-3-(4-

fluorophenyl)propyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone (2.04 g, 4.98 mmol) and dimethylaminopyridine (DMAP) (1.46 g, 11.96 mmol) in tetrahydrofuran (THF) (15 mL). After TLC (5% CH_3OH/toluene) indicates consumption of starting material (10 min), dilute the mixture with ether (Et_2O), wash with 1M HCl and brine, dry over anhydrous Na_2SO_4, concentrate to a clear foam 2.47 g (100%) and use without further purification. NMR (400 MHz, $CDCl_3$): 7.33(2H, d, J=8.6 Hz), 7.27(2H, m), 7.21(2H, m), 7.11(2H, d, J=8.5 Hz), 7.02(2H, t, J=8.6 Hz), 6.94(2H, d, J=8.5 Hz), 5.70(1H, t, J= 7Hz), 4.60(1H, d, J=2.4 Hz), 3.06(1H, dt, J=7.9, 2.4 Hz), 2.31(3H, s), 2.06(3H, s), 2.03(1H, m), 1.86(2H, M). HRMS (FAB): calcd. for M+H: $C_{28}H_{25}NO_5F_2$, 493.1701; found 493.1695.

Step 2: Add sodium ethoxide (0.338 g, 4.97 mmol) to a room temperature solution of guanadine hydrochloride (0.499 g, 5.22 mmol) in CH_3OH (15 mL). After 10 min, slowly add the resulting solution by pipette to a solution of the product of Step 1 (2.45 g, 4.97 mmol) in CH_3OH (15 mL). Monitor the reaction by TLC (15% EtOAc/toluene), and upon consumption of starting material (~1h), concentrate the mixture at room temperature in vacuo. Redissolve the resulting residue in ethyl acetate (EtOAc) and concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with 15% EtOAc/toluene. Elute with the same solvent to obtain 1.31 g (95%) of the title compound as a glass. HRMS (FAB): calcd. for M+H: $C_{26}H_{24}NO_4F_2$, 452.1673; found 452.1661.

Preparation A2

Trans-(3R,4S)-1-(4-(benzoyl)phenyl)-3-(3-phenyl)propyl]-4-(4-hydroxy)phenyl-2-azetidinone

Step 1: Reflux a mixture of 4-nitrobenzophenone (20.94 g, 92.2 mmol), ethylene glycol (25.6 mL, 461 mmol), p-toluenesulfonic acid (0.87 g, 4.61 mmol) and toluene (125 mL) overnight with azeotropic removal of water via a Dean-Stark trap. Cool the mixture to room temperature, dilute with Et_2O, wash with 1N NaOH, water and brine, dry over anhydrous Na_2SO_4 and concentrat to obtain 24.81 g (99%) of a white solid. NMR (400 MHz, $CDCl_3$): 8.18(2H, d, J=9.0 Hz), 7.12(2H, d, J= 9.0 Hz), 7.50(2H, d, J=8.0 Hz), 7.34(3H, m), 4.09(4H, m).

Step 2: Dissolve the product of step 1 (24.8 g, 92 mmol) in EtOAc (75 mL), dilute with ethanol (75 mL) and purge with N_2. Wash Raney nickel (~40 g) three times with ethanol and transfer to the reaction flask. Hydrogenate the resulting mixture on a Parr shaker at 60 psi until TLC (30% EtOAc/hexanes) indicates consumption of starting material (<2h). Filter the mixture through celite under a blanket of N_2. Wash the filter cake with 50% EtOAc/ethanol and concentrate the filtrate to give 21.6 g (97%) of a solid. NMR (400 MHz, $CDCl_3$): 7.50(2H, d, J=8.0 Hz), 7.30(5H, m), 6.66(2H, d, J=8.6 Hz),4.03(4H, m).

Step 3: Dissolve the product of step 2 (8.49 g, 35.2 mmol) and 4-(benzyloxy)benzaldehyde (7.47 g, 35.2 mmol) in hot isopropanol (150 ml). Heat the mixture to reflux and allow the isopropanol to escape until a volume of 75 mL is obtained. Dilute the resulting solution with hexanes (200 mL) and allow to stand overnight. Collect the resultant crystals, wash with hexanes and dry under vacuum to give 14.4 g (95%) of white crystals. NMR (400 MHz, $CDCl_3$): 8.36(1H, s), 7.54(4H, m), 7.37(8H, m), 7.08(2H, m), 5.15(2H, s), 4.08(4H, s). MS(CI) 436(M+H, 78), 358(39), 149(100).

Step 4: Add 5-phenylvaleryl chloride (10.7 mL, 53.1 mmol) to a refluxing solution of the product of step 3 (15.4 g, 35.4 mmol) and n-tributylamine (25.3 mL, 106.3 mmol) in toluene (350 mL) and reflux overnight. Cool the mixture to room temperature, quench with 1 M HCl, dilute with EtOAc, wash with 1M HCl, $NaHCO_3$ (sat), water and brine, dry over anhydrous Na_2SO_4 and concentrate onto enough silica gel such that a free flowing powder results. Load the powder onto a chromatography column prepacked with 20% EtOAc/hexanes and elute with the same solvent to obtain 14 g of a solid. Recrystallize from EtOAc/hexanes to obtain 8.54 g (40%) of white crystals. NMR (400 MHz, $CDCl_3$): 7.30(21H, m), 6.94(2H, d, J=8.6 Hz), 5.03(2H, s), 4.54(1H, d, J=2.4 Hz), 4.01(4H, s), 3.07(1H, s), 2.63(2H, t, J=7.0 Hz), 1.92(1H, m), 1.81(3H, m).

Step 5: Add 6N HCl (30 mL) to a solution of the product of step 4 (4.4 g, 7.4 mmol) in THF (120 mL). After 7h, dilute with EtOAc, wash with $NaHCO_3$ (sat) and brine, dry over anhydrous Na_2SO_4 and concentrate to giv 4.11 g (100%) of a white glass. NMR (400 MHz, $CDCl_3$): 7.72(4H, m), 7.55(1H, m), 7.40(8H, m), 7.27(3H, m), 7.18(3H, m), 6.98(2H, d, J=8.8 Hz), 5.05(2H, s), 4.65(1H, d, J=2.44 Hz), 3.16(1H, m),

2.65(2H, t, 7.6 Hz), 1.98(1H, m), 1.85(3H, m). HRMS(FAB) calcd for M+H, $C_{38}H_{34}NO_3$: 552.2539, found 552.2541.

Step 6: Add boron trichloride-dimethylsulfide (14 mL, 28.3 mmol, 2M in CH_2Cl_2) to a room temperature solution of the product of step 5 (1.56 g, 2.83 mmol) in CH_2Cl_2 (30 mL). When TLC (20% EtOAc/hexane) indicates consumption of starting material, quench the reaction by the addition of $NaHCO_3$ (sat). Dilute the resulting mixture with EtOAc, wash with $NaHCO_3$ (sat) and brine, dry over anhydrous Na_2SO_4 and concentrate onto enough silica gel such that a free flowing powder results. Load the powder onto a chromatography column prepacked with 33% EtOAc/hexanes and elute with the same solvent to obtain 1.02 g (78%) of a white glass. NMR (400 MHz, $CDCl_3$): 7.73(4H, m), 7.56(1H, t, 7.6 Hz), 7.45(2H, t, J=7.6 Hz), 7.34(2H, d, J=8.6 Hz), 7.28(3H, m), 7.2(2H, m), 7.16(2H, d, J=7.3 Hz), 6.85(2H, d, J=8.3 Hz), 4.65(1H, d, J=2.4 Hz), 3.15(1H, m), 2.65(2H, t, J=7.6 Hz), 1.98(1H, m), 1.85(3H, m).

Step 7: Add acetic anhydride (0.43 mL, 4.51 mmol) to a room temperature solution of the product of step 6 (1.61 g, 3.75 mmol) and N,N-dimethylaminiopyridine (0.69 g, 5.64 mmol) in CH_2Cl_2 (20 mL). When TLC (30% EtOAc/hexanes) indicates consumption of starting material, dilute with EtOAc, wash with 1M HCl, water and brine, dry over anhydrous Na_2SO_4 and concentrate onto enough silica gel such that a free flowing powder results. Load the powder onto a chromatography column prepacked with 30% EtOAc/hexanes and elute with the same solvent to obtain 1.64 g (78%) of a white glass. Chiral preparative HPLC (Chiracel OD column, 20% EtOH/hexanes, 65 mL/min) provided 0.55 g of enantiomer A and 0.93 g of enantiomer B. NMR (400 MHz, $CDCl_3$): 7.73(4H, m), 7.56(1H, t, J=7.2 Hz), 7.46(2H, t, J=7.7 Hz), 7.32(6H, m), 7.19(3H, m), 7.12(2H, d, J=8.4 Hz), 4.70(1H, d, J=2.44 Hz), 3.17(1H, m), 2.67(2H, t, J=7.6 Hz), 2.31(3H, s), 1.97(1H, m), 1.86(3H, m). MS(CI) 504(M+H, 100), 224(100). Analytical HPLC (Chiracel OD, 20% EtOH/ hexanes, 1.0 mL/min) Enantiomer A, Rt=16.83 min, Enantiomer B, Rt=23.83 min.

Step 8: Dissolve LiOH (0.098 g, 2.35 mmol) in water (2.5 mL) and add to a solution the product of step 7, enantiomer B (0.91 g, 1.8 mmol) in THF (7.5 ml). Stir ov might until TLC(30% EtOAc/h xanes) indicates consumption of starting mat rials. Quench the reaction with 1 M HCl,

dilute with EtOAc, wash with 1 M HCl, water and brine, dry over anhydrous Na_2SO_4 and concentrate onto enough silica gel such that a free flowing powder results. Load the powder onto a chromatography column prepacked with 30% EtOAc/hexanes and elute with the same solvent to obtain 0.36 g (46%) of a white glass. Analytical HPLC (Chiracel AS, 20% EtOH/hexanes, 0.5 mL/min), Rt=26.81 min. NMR (400 MHz, $CDCl_3$): 7.77(4H, m), 7.56(1H, t, J=7.6 Hz), 7.45(2H, t, J=7.6 Hz), 7.34(2H, d, J=8.6 Hz), 7.28(2H, m), 7.21(3H, m), 7.16(2H, d, J=7 Hz). 6.85(2H, d, J=8.4 Hz). 4.65(1H, d, J=2.4 Hz), 3.15(1H, m), 2.65(2H, t, J=7.4 Hz), 1.98(1H, m), 1.85(3H, m).

Preparation B

Methyl (2,3,4-tri-O-acetyl-D-glucopyransyl)uronate 1-(2,2,2,-trichloroacetimidate)

Add Cs_2CO_3 (0.49 g, 1.5 mmol) to a room temperature solution of methyl 2,3,4-tri-O-acetyl-D-glucopyranuronate (5.0 g, 15 mmol) and trichloroacetonitrile (3.75 mL, 37.4 mmol) in CH_2Cl_2 (48 mL). and stir overnight. Filter the resulting brown solution through a cotton plug, washed the filtrate with water, dry over anhydrous Na_2SO_4 and concentrate. Dissolve the residue in EtOAc and concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with 30% EtOAc/hexanes. Elute with the same solvent and take only the cleanest fractions to obtain 4.35 g (61%) of the title compound as a glass. NMR (400 MHz, $CDCl_3$): 8.74(1H, s), 6.65(1H, d, J=3.7 Hz), 5.64(1H, t, J=9.8 Hz), 5.27(1H, t, J=9.5 Hz), 5.15(1H, dd, J=3.6, 10 Hz), 4.50(1H, d, J=10.1 Hz), 3.76(3H, s), 2.06(6H, s), 2.02(3H, s).

In a similar manner prepare:

Preparation B2

2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-B-D-glucopyranosyl)-α-D-glucopyranosyl 1-(2,2,2,-trichloroacetimidate)

NMR (400 MHz, $CDCl_3$): 8.66(1H, s), 6.49(1H, d, J=3.7 Hz), 5.53(1H, t, J=10 Hz), 5.12(3H, m), 4.94(1H, t, J=8.2 Hz), 4.53(2H, m), 4.40(1H, dd, J=4.2, 12.6 Hz), 4.12(2H, m), 4.05(1H, dd, J=2.1, 12.5 Hz), 3.85(1H. t, J=9.4 Hz), 3.67(1H, m), 2.12(3H, s), 2.10(3H, s), 2.05(3H, s), 2.04(3H, s), 2.02(3H, s), 2.01(3H, s), 2.00(3H, s).

Preparation B3

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl 1-(2,2,2,-Trichloroacetimidate)

NMR (400 MHz, $CDCl_3$): 8.70(1H. s), 6.57(1H, d, J=3.8 Hz), 5.57(1H, t, J=9.8 Hz), 5.19(1H, t, J=9.8 Hz), 5.14(1H, dd, J=3.7, 10.2 Hz), 4.29(1H, dd, J=4, 12.2 Hz), 4.22(1H, m), 4.13(1H, m), 2.09(3H, s), 2.06(3H, s), 2.04(3H, s), 2.03(3H, s). MS(Electrospray): 509($M+NH_4$).

Example 1

1-O-[4-[Trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid

Step 1: 2,3,4-Tri-O-acetyl-1-O-[4-[trans-(3R,4S)-3-[3-[(S)-acetyloxy-3-(4-fluorophenyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyranuronic acid methyl ester

Add boron trifluoride etherate (0.091 mL, 0.74 mmol) to a -25 °C solution of the product of Preparation A (3.33 g, 7.38 mmol) and Preparation B (4.24 g, 8.86 mmol) in CH_2Cl_2 (74 mL) and maintain the reaction at -20 °C for 2h. Allow the reaction to warm to 10 °C over 2h. Quench the mixture with saturated NH_4Cl, dilute with EtOAc, wash with saturated NH_4Cl, water and brine, dry over anhydrous Na_2SO_4 and concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with 40% EtOAc/hexanes. Elute with the same solvent to obtain 5.39 g (95%) as a foam. NMR (400 MHz, $CDCl_3$): 7.26(4H, m), 7.21(2H, m), 7.01 (4H, m), 6.93(2H, t, J=8.4 Hz), 5.69(1H, t, J= 6.7 Hz), 5.34(2H, m), 5.29(1H, m), 5.15(1H, d, J=7.2 Hz), 4.56(1H, d, J=2.1 Hz), 4.17(1H, m), 3.73(3H, s), 3.02(1H, dt, J=7.6, 2.3 Hz), 2.07(14H, m), 1.85(2H, m). HRMS (FAB): calcd. for M+H: $C_{39}H_{40}NO_{13}F_2$, 768.2468; found 768.2460.

Step 2: Dissolve the product of Step 1 (5.08 g, 6.98 mmol) in a mixture of CH_3OH (127 mL) and triethylamine (Et_3N) (127 mL) at room temperature. Slowly add water (445 mL) via an addition funnel over 10 min in order to maintain a homogeneous solution, then stir the resulting clear yellow solution over night. Quench a small aliquot of the reaction mixture in a vial containing 1 M HCl and EtOAc and monitor consumption of the starting material by TLC (5% acetic acid (HOAc)/20% CH_3OH/75% CH_2Cl_2) of the EtOAc layer. Remove the CH_3OH and Et_3N

on a rotary evaporator, acidify the remaining solution with 1M HCl, dilute with EtOAc and extract with EtOAc. Combine the extracts, wash with 1M HCl, water and brine, dry over anhydrous Na_2SO_4 and concentrate to a white solid 3.82 g (93%). Dissolve the solid in CH_2Cl_2, and concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with silica and 15% CH_3OH/CH_2Cl_2. Elute with 5% HOAc/15% CH_3OH/80% CH_2Cl_2. Concentrate the fractions containing the title compound, azeotrope first with toluene (3X) and then CH_3OH (5X). Heat the resultant solid to 60°C under vacuum to remove any residual solvent and obtain the title compound as a white solid 2.6 g (64%). NMR (400 MHz, CD_3OD): 7.29(6H, m), 7.09(1H, d, J=8.6 Hz), 6.70(4H, m), 4.96(1H, m), 4.80(1H, d, J=2.0 Hz), 4.59(1H, m), 3.97(1H, d, J=9.6 Hz), 3.59(1H, m), 3.49(2H, m), 3.09(1H, m), 1.86(4H, m). HRMS (FAB): calcd. for M+H: $C_{30}H_{30}NO_9F_2$, 586.1889; found 586.1883.

Example 1A

1-O-[4-[Trans-(3R,4S)-1-(4-iodophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid

Treat 1-(4-iodophenyl)-3(R)-[3(S)-acetyloxy-3-(4-fluorophenyl)-propyl)]-4(S)-(4-hydroxyoxyphenyl)-2-azetidinone and the product of Preparation B according to the procedure described in Example 1 to obtain the title compound. M.p. 135-137 °C; FAB MS calc'd for $C_{30}H_{29}FINO_9$ NaCl m/z = 751.05, found m/z = 751.2.

Example 2

1-O-[4-[Trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-3-O-(Beta-D-glucpyranosyl)-Beta-D-glucopyranose

Step 1: 2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-B-D-gluco-pyranosyl)-1-O-[4-[trans-(3R,4S)-3-[3(S)-acetyloxy-3-(4-fluorophenyl)-propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyran

Using a procedure similar to that described in Example 1, Step 1, combine the product of Preparation A and Preparation B2 to obtain the title compound of Step 1. NMR (400 MHz, $CDCl_3$): 7.23(6H, m), 6.97(6H, m), 5.69(1H, t, 6.6 Hz), 5.26(1H, t, J=9.1 Hz), 5.11(4H, m), 4.95(1H, t, J=8.2 Hz), 4.54(3H, m), 4.39(1H, dd, J=4.3, 12.5 Hz), 4.06(2H, m), 3.87(1H, t, J=9.5 Hz), 3.75(1H, m), 3.68(1H, m), 3.02(1H, dt, J=2.1,

7.6 Hz), 2.05(26H, m), 1.85(2H, m). HRMS (FAB): calcd. for M+Na: $C_{52}H_{57}NO_{21}F_2Na$, 1092.3289; found 1092.3308.

Step 2: Using a procedure similar to that described in Example 1, Step 2, treat the product of Step 1, above, to obtain the title compound of Example 2. NMR (400 MHz, CD_3OD: 7.29(6H, m), 7.10(2H, d, J=8.7 Hz), 7.01(4H, m), 4.96(1H, under CD_3OD), 4.81(1H, d, J=2.2 Hz), 4.60(1H, m), 4.43(1H, d, J=7.9 Hz), 3.88(3H, m), 3.62(4H, m), 3.51(1H, d, J=8.9 Hz), 3.34(2H, m), 3.24(1H, t, J=8.8 Hz), 3.08(1H, m), 1.88(7H, m). MS (FAB): 756 (M+Na, 70), 734(M+, 100), 716(716, 20).

Example 3

1-O-[4-[Trans-(3R,4S)-3-[3(S)-hydroxy-3-(4-fluorophenyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyranose

Step 1: 2,3,4,5-Tetra-O-acetyl-1-O-[4-[trans-(3R,4S)-3-[3(S)-acetyloxy-3-(4-fluorophenyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyran

Using a procedure similar to that described in Example 1, Step 1, combine the product of Preparation A and Preparation B3 to obtain the title compound of Step 1. NMR (400 MHz, $CDCl_3$): 7.26(4H, m), 7.20 (2H, m), 7.01(4H, m), 6.93(2H, t, J=8.5 Hz), 5.69(1H, t, J=6.5 Hz), 5.29 (2H, m), 5.18(1H, t, J=9.7 Hz), 5.09(1H, d, J=7.3 Hz), 4.56(1H, d, J=2.2 Hz), 4.29(1H, dd, J=5.2, 12.2 Hz), 4.17(1H, dd, J=2.2 Hz, 12.2 Hz), 3,85 (1H, m), 3.03(1H, dt, J=2.1, 7.5 Hz), 2.06(17H, m), 1.85 (2H, m). HRMS (FAB): calcd. for M+Na: $C_{40}H_{41}NO_{13}F_2Na$, 804.2444, found 804.2432.

Step 2: Using a procedure similar to that described in Example 1, Step 2, treat the product of Step 1, above, to obtain the title compound of Example 3. NMR (400 MHz, CD_3OD): 7.29(6H, m), 7.11(2H, d, J=8.8 Hz), 6.98(4H, m), 4.89(1H, under CD_3OD), 4.80(1H, d, J=2.2 Hz), 4.60 (1H, m), 3.88(1H, dd, J=2.0, 12.0 Hz), 3.68(1H, dd, J=5.4, 12.0 Hz), 3.41 (3H, m), 3.08(1H, m), 1.86(4H, m). MS (FAB): 572 (M+H, 40), 392(100).

Example 4

1-O-[4-[Trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester

Add KCN (0.028 g, 0.43 mmol) to a room temperature solution of the product of Example 1, Step 1, (0.312 g, 0.43 mmol) in CH_3OH (5 mL) and stir th mixture overnight. Monitor by TLC (10% CH_3OH/CH_2Cl_2);

heat the mixture to 40 °C for 2.5 h. Cool the mixture to room temperature, concentrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with silica and 5% CH_3OH/CH_2Cl_2. Elute with 5% CH_3OH/CH_2Cl_2 and collect the purest fractions to obtain 0.116 g of the title compound. NMR (400 MHz, $CDCl_3/CD_3OD$): 7.16(6H, m), 6.95(4H, m), 6.86(2H, t, J=8.6 Hz), 4.83(1H, d, J=7.6 Hz), 4.56(1H, t, J=6.3 Hz), 4.55(1H, d, J=2.1 Hz), 3.90(1H, d, J=9.8 Hz), 3.73(3H, s), 3.67(1H, t, J=9.1 Hz), 3.51(1H, m), 3.46(1H, t, J=9.2 Hz), 3.30(1H, s), 2.98(1H, m), 1.80(4H, m). HRMS (FAB): calcd. for M+H: $C_{31}H_{32}NO_9F_2$, 600.2045; found 600.2049.

Example 5

1-O-[4-[Trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenyl)propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester

Step 1: 2,3,4-Tri-O-acetyl-1-O-[4-[Trans-(3R,4S)-3-[3-[(S)-acetyloxy-3-(4-fluorophenyl)propyl-1-(4-methoxyphenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyranuronic Acid Methyl Ester

Add triphenylphosphine (0.19 g, 0.72 mmol) to a 0 °C solution of 1,1'-(azodicarbonyl)dipiperdine (0.18 g, 0.72 mmol) in THF (3 mL). After 10 min, add (3R,4S)-4-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone (0.2 g, 0.52 mmol), followed by methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate (0.21 g, 0.62 mmol). Allow the mixture to warm to room temperature overnight. Concentrate the mixture onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with silica and 30% EtOAc/hexanes. Elute with 30-50% EtOAc/hexanes to obtain 0.198 g of material which is further purified by silica chromatography eluting with 20% CH_3OH/CH_2Cl_2 to provide 0.074 g of the title compound of Step 1. NMR (400 MHz, $CDCl_3$): 7.27(4H, m), 7.17(5H, m), 6.98(2H, J=8.5 Hz), 6.77(2H, m), 5.30(3H, m), 5.13(1H, d, J=7.3 Hz), 4.56(1H, d, J=1.9 Hz), 4.17(1H, m), 3.74(3H, s), 3.73(3H, s), 3.04(1H, m), 2.64(2H, t, J=7.6 Hz), 2.05(9H, m), 1.97(1H, m), 1.82(3H, m). HRMS (FAB): calcd. for M+H: $C_{38}H_{42}NO_{12}$ 704.2707; found 704.2696.

Step 2: Using a procedure similar to that of Example 4, tr at the product of Step 1 to obtain the title compound. NMR (400 MHz, $CDCl_3$): 7.27(4H, m), 7.17(5H, m), 7.04(2H, J=8.6 Hz), 6.75(2H, J=9.1 Hz),

4.90(1H, d, J=7.0 Hz), 4.55(1H, d, J=1.8 Hz), 3.98(1H, d, J=9.7 Hz), 3.88(1H, t, J=8.6 Hz), 3.76(8H, m), 3.03(1H, m), 2.63(2H, t, J=6.7 Hz), 1.95(1H, m), 1.81(3H, m). HRMS (FAB): calcd. for M+H: $C_{32}H_{36}NO_9$, 578.2390; found 578.2379.

Example 6

1-O-[4-[Trans-(3R,4S)-1-(4-(benzoyl)phenyl)-2-oxo-3-(3-phenyl)propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester

Step 1: 2,3,4-Tri-O-acetyl-1-O-[4-[Trans-(3R,4S)-1-(4-(benzoyl)phenyl)-2-oxo-3-(3-phenyl)propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester

In a similar manner to Example 5, Step 1, treat (3R,4S)-1-(4-benzoylphenyl)-4-(4-hydroxyphenyl)-3-(3-phenylpropyl)-2-azetidinone and methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate to obtain the title compound of Step 1. NMR (400 MHz, $CDCl_3$): 7.73(4H, m), 7.57(1H, t, J=7.0 Hz), 7.46(2H, t, J=8.0 Hz), 7.30(6H, m), 7.21(1H, d, J=7.1 Hz), 7.16 (2H, d, J=8.0 Hz), 7.01(2H, d, J=8.5 Hz), 5.31(3H, m), 5.15(1H, d, J=7.3 Hz), 4.67(1H, d, J=2.2 Hz), 4.17(1H, dd, J=2.7, 6.7 Hz), 3.73(3H, s), 3.14 (1H, m), 2.66(2H, t, J=7.4 Hz), 2.06(9H, m), 1.98(1H, m), 1.85(3H, m). HRMS (FAB): calcd. for M+H: $C_{44}H_{44}NO_{12}$, 778.2864; found 778.2849.

Step 2: Using a procedure similar to that of Example 4, treat the product of Step 1 to obtain the title compound. NMR (400 MHz, $CDCl_3$): 7.72(2H, overlapping d, J=8.6, 7.6 Hz), 7.56(1H, t, J=7.6 Hz), 7.45(2H, t, J=7.7 Hz), 7.30(6H, m), 7.20(1H, d, J=7.0 Hz), 7.16(2H, d, J=7.6 Hz), 7.08(2H, d, J=8.6 Hz), 4.93(1H, d, J=7.0 Hz), 4.67(1H, dd, J=2.1 Hz), 3.99(1H, d, J=9.8 Hz), 3.88(1H, t, J=8.6 Hz), 3.81(3H, s), 3.73(2H, m), 3.14(1H, m), 2.65(2H, t, J=7.6 Hz), 1.98(1H, m), 1.84(3H, m). HRMS (FAB): calcd. for M+H: $C_{38}H_{38}NO_9$, 652.2547; found 652.2528.

Example 7

1-O-[4-[Trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-Beta-D-glucopyranose

Step 1: 1-O-[4-[Trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-2,3,4,6,-tetra-O-(phenylmethyl)-Beta-D-glucopyranose

Add n-tributylphosphine (1.45 mL, 5.81 mmol) to a 0 °C solution of 1,1'-(azodicarbonyl)dipiperdine (1.47 g, 5.81 mmol) in THF (30 mL). After 5 min., add (3R,4S)-4-(4-hydroxyphenyl)-1-(4-methoxy-phenyl)-3-

(3-phenylpropyl)-2-azetidinone (1.5 g, 3.87 mmol), followed by 2,3,4,6-tetra-O-benzyl-D-glucopyranose (2.72 g, 5.03 mmol). The reaction becomes very thick, and additional THF (30 mL) is added to facilitate stirring; the mixture is allowed to warm to room temperature overnight. Filter the mixture through celite, wash the filter cake with EtOAc, and concentrate the filtrate onto enough silica such that a free flowing powder is obtained. Load the resulting powder onto a chromatography column packed with silica and 5% EtOAc/toluene. Elute with the same solvent to obtain 3.57 g (~100%) of the title compound of Step 1 as a thick syrup. NMR (400 MHz, $CDCl_3$): 7.16(19H, m), 7.19(10H, m), 7.04(2H, d, J=8.7 Hz), 6.76(2H, d, J=9.2 Hz), 4.98(3H, m), 4.83(3H, m), 4.55(4H, m), 3.70(9H, m), 3.05(1H, m), 2.65(2H, t, J=7.3 Hz), 1.96(1H, m), 1.83(3H, m). MS (FAB): 910(M+, 55), 568(40), 478(100), 386(55).

Step 2: Dissolve the product of Step 1 (0.20 g, 0.35 mmol) in CH_3OH (4.5 mL), dilute with EtOAc (4.5 mL) and purge with nitrogen. Add 20% $Pd(OH)_2$ on carbon (0.35 g), purge the resulting mixture with hydrogen (3X) and then stir under a balloon of hydrogen overnight. Filter the mixture through celite and wash the filter cake with EtOAc followed by CH_3OH. Concentrate the filtrate to a clear foam 0.161 g (83% crude). Purify the foam further by silica chromatography eluting with 5% CH_3OH/EtOAc to obtain 0.127 g (66%) of the the title compound as a white powder. NMR (400 MHz, CD_3OD): 7.18(11H, m), 6.78(2H, d, J=8.9 Hz), 4.88(1H, partially obscured by CD_3OD), 4.72(1H, d, J=1.2 Hz) 3.88(1H, d, J=11.7 Hz), 3.70(4H, m), 3.41(4H, m), 3.03(1H, m), 2.60(2H, t, J=7.0 Hz), 1.79(4H, m). HRMS (FAB): calcd. for M+H: $C_{31}H_{36}NO_8$, 550.2441; found 500.2424.

Example 8

1-O-[4-[Trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-Beta-D-glucuronic acid

Step 1: 2,3,4-tri-O-Benzyl-1-O-[4-[trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid benzyl ester

Use (3R,4S)-4-(4-hydroxyphenyl)-1-(4-methoxy-phenyl)-3-(3-phenylpropyl)-2-azetidinon and benzyl 2,3,4-tri-O-benzyl-D-gluco-pyranur nat in a procedure similar to that described in Example 7, Step 1, to obtain th title compound of Step 1. NMR (400 MHz, $CDCl_3$):

7.22(29H, m), 7.01(2H, d, J=8.7 Hz), 6.77(2H, d, J=9.1 Hz), 5.15(2H, app. d, J=3.8 Hz), 5.01(1H, d, J=7.2 Hz), 4.97(1H, d, J=11 Hz), 4.90(1H, d, J=11 Hz), 4.80(2H, d, J=11 Hz), 4.74(1H, d, J=10.7 Hz), 4.56(1H, d, J=2.2 Hz), 4.50(1H, d, J=10.7 Hz), 4.04(1H, d, J=9.6 Hz), 3.93(1H, t, J=8.6 Hz), 3.73(5H, m), 3.05(1H, m), 2.65(2H, t, J=7.6 Hz), 1.96(1H, m), 1.83(3H, m). HRMS (FAB): calcd. for M+H: $C_{59}H_{58}NO_9$ 924.4112; found 924.4119.

Step 2: Using a procedure similar to Example 7, Step 2, treat the product of Step 1 to obtain the title compound of Example 8. NMR (400 MHz, CD_3OD): 7.31(2H, d, J=8.9 Hz), 7.21(7H, m), 7.09(2H, d, J=8.7 Hz), 7.81(2H, d, J=8.9 Hz), 4.97(1H, dd, J=1.9, 5.5 Hz), 4.76(1H, d, J=2.0 Hz), 3.97(1H, d, J=9.7 Hz), 3.72(3H, s), 3.60(1H, m), 3.49(2H, m), 3.08(1H, m), 2.64(2H, t, J=7.2 Hz), 1.83(4H, m). HRMS (FAB): calcd. for M+H: $C_{31}H_{34}NO_9$ 564.2234; found 564.2242.

Example 9

1-Methyl-6-O-[4-[trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-Alpha-D-glucopyranoside

Step 1: 1-Methyl-2,3,4-tri-O-Benzyl-6-O-[4-[Trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-Alpha-D-glucopyranoside

Use (3R,4S)-4-(4-hydroxyphenyl)-1-(4-methoxy-phenyl)-3-(3-phenylpropyl)-2-azetidinone and methyl 2,3,4-tri-O-benzyl-D-gluco-pyranoside in a procedure similar to that described in Example 7, Step 1, to obtain the title compound of Step 1. NMR (400 MHz, $CDCl_3$): 7.26(24H, m), 6.85(2H, d, J=8.6 Hz), 6.74(2H, d, J=9 Hz), 5.01(1H, d, J=10.7 Hz), 4.86(1H, d, J=11.0 Hz), 4.85(1H, d, J=10.7 Hz), 4.82(1H, d, J=12.1 Hz), 4.69(1H, d, J=12.1 Hz), 4.63(1H, d, J=3.6 Hz), 4.54(1H, d, J=2.3 Hz), 4.51(1H, d, J=11.0 Hz), 4.09(2H, d, J=2.8 Hz), 4.03(1H, t, J=9.6 Hz), 3.90(1H, d, J=10.1 Hz), 3.72(3H, s), 3.60(1H, dd, J=3.6, 9.6 Hz), 3.38(3H, s), 3.06(1H, m), 2.64(2H, t, J=7.6 Hz), 1.97(1H, m), 1.83(3H, m).

Step 2: Using a procedure similar to Example 7, Step 2, treat the product of Step 1 to obtain the titl compound of Example 9. NMR (400 MHz, $CDCl_3$): 7.22(9H, m), 6.94(2H, d, J=8.6 Hz), 6.76(2H, d, J=8.9 Hz), 4.81(1H, d, J=3.9 Hz), 4.54(1H, d, J=2.2 Hz), 4.22(2H, m), 3.97(1H, m), 3.71(5H, m), 3.56(1H, dd, J=3.9, 9.1 Hz), 3.44(3H, s), 3.06(1H, m),

2.64(2H, d, J=7.4 Hz), 1.91(1H, m), 1.82(3H, m). HRMS (FAB): calcd. for M+H: $C_{32}H_{38}NO_8$ 564.2597, found 564.2578.

Example 10

1-O-[4-[Trans-(3R,4S)-1-(4-(benzoyl)phenyl)-2-oxo-3-(3-phenyl)propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid

Add LiOH (0.6 mL, 0.6 mmol, 1M) to a room temperature solution of the product of Example 6 (0.064 g, 0.1 mmol) in THF (2 mL). After 50 min., dilute the mixture with EtOAc, quench with HCl (1M), wash with HCl (1M) and brine, dry over anhydrous Na_2SO_4 and concentrate to a white foam 0.60 g (97%). NMR (400 MHz, CD_3OD): 7.67(4H, m), 7.60(1H, m), 7.48(3H, m), 7.36(2H, d, J=8.8 Hz), 7.34(2H, d, J=8.8 Hz), 7.23(2H, m), 7.14(2H, d, J=7.5 Hz), 7.10(2H, d, J=8.7 Hz), 4.97(1H, m), 4.87(1H, d, J=2.2 Hz), 3.97(1H, d, J=9.7 Hz), 3.60(1H, m), 3.49(2H, m), 3.17(1H, m), 2.63(2H, t, J=7.4 Hz), 1.89(1H, m), 1.81(3H, m). HRMS (FAB): calcd. for M+H: $C_{37}H_{36}NO_9$ 638.2390; found 638.2377.

Example 11

1-O-[4-[Trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-iodophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid

Step 1: Condense 1-(4-fluorophenyl)-3(R) -[3(S)-acetyloxy-3-(4-bromo-phenyl)propyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone and the product of Preparation B with boron trifluoride etherate according to the procedure described in Example 1. To a solution of the resultant tetraacetate (250 mg, 0.30 mmol) in CH_3OH (2 mL) cooled to 0°C, add KCN (10 mg, 0.15 mmol) and stir at room temperature for 2h, then heat to 45°C for 4.5h. Cool the mixture to room temperature and partition between water (20mL) and EtOAc (30 mL). Wash the EtOAc layer with water and brine, dry (Na_2SO_4) and concentrate in vacuo. Adsorb the residue (230 mg) onto SiO_2 and chromatograph over SiO_2 (25 g), eluting with 2% CH_3OH in CH_2Cl_2 progressing to 10% CH_3OH in CH_2Cl_2 to give, after concentration, 84 mg (43%) of the aryl bromide as a solid.

Step 2: To the product of step 1 (25 mg, 0.038 mmol) dissolved in degassed DMF (0.4 mL), add hexabutylditin (220 mg, 38 mmol) and t trakis triphenylphosphine palladium (4.4 mg. 0.0038 mmol) and heat th mixture to 95°C under argon for 5h. Cool the reaction, concentrate in vacuo and adsorb the resulting r sidu directly onto SiO_2.

Chromatograph over SiO_2 (4g), eluting with CH_2Cl_2 progressing to 10% CH_3OH in CH_2Cl_2. Rechromatograph the desired fraction as above and after concentration obtain 7.4 mg (22%) of the desired aryl stannane as a waxy solid.

Step 3: To the product of step 2 (11.8 mg, 0.0135 mmol) dissolved in CH_3OH (2 mL) containing pH 5.8 phosphate buffer (0.3mL), add a 1M solution of NaI in water (14mL, 0.014 mmol). To this mixture add 68 iodobeads® (~37 mmol) and gently shake the resulting mixture for 1.5h at room temperature. Filter the iodobeads and wash with EtOH and a small amount of ether. Concentrate the filtrate and partition the residue between EtOAc and 10% aqueous Na_2SO_3, dry the EtOAc layer ($MgSO_4$) and concentrate in vacuo. Adsorb the residue onto SiO_2 and chromatograph over SiO_2 (2g), eluting with CH_2Cl_2 progressing to 6% CH_3OH in CH_2Cl_2. Concentrate the appropriate fractions to obtain 6.1 mg (64%) of the methyl ester of the title compound as a solid.

Step 4: Stir a solution of the product of step 3 (6.1 mg, 8.6mmol) in a mixture of water (0.7mL), triethylamine (0.2 mL) and CH_3OH (0.1 mL) at room temperature for 30 min. Concentrate the mixture in vacuo to give 5 mg (83%) of the title compound as a solid. M.p. 157 - 159 °C, FAB MS calc'd for $C_{30}H_{30}FINO_9$ m/z = 694.1, found m/z = 694.1.

The following formulations exemplify some of the dosage forms of this invention. In each, the term "active compound" designates a compound of formula I.

EXAMPLE A - Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules.

Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B - Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

The in vivo activity of the compounds of formula I can be determined by the following procedure.

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

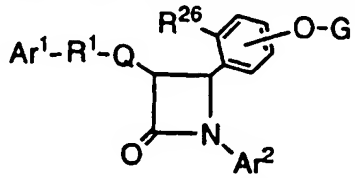
Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the presence of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by IM injection of ketamine and sacrificed by decapitation. Blood is collected into Vacutainer™ tubes containing EDTA for plasma total cholesterol and triglyceride analysis and the liver excised for free and esterified

cholesterol and triglyceride tissue analysis. Data is reported as percent reduction of plasma cholesterol and hepatic cholesterol esters versus control levels.

Using the test procedures described above, the following in vivo data were obtained for compounds of formula I. Data is reported as percent change (i.e., percent reduction in plasma cholesterol and in hepatic cholesterol esters) versus control, therefore, negative numbers indicate a positive cholesterol-lowering effect. For racemic compounds of formula I or active diastereomers or enantiomers of compounds of formula I, compounds administered at dosages of 3 to 10 mg/kg show a range of 0 to -98% reduction in hepatic cholesterol esters, while compounds administered at dosages of 0.01 to 1 mg/kg show a range of -19 to -94% reduction in hepatic cholesterol esters. Compounds preferably show a range of -50 to -98% reduction in hepatic cholesterol esters at a dosage range of 0.01 to 1 mg/kg.

We claim:

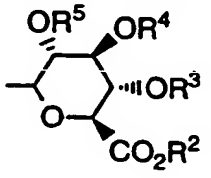
1. A compound represented by the structural formula



or a pharmaceutically acceptable salt thereof, wherein

R^{26} is H or OG^1;

G and G^1 are independently selected from the group consisting of H,



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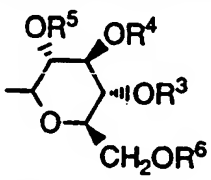

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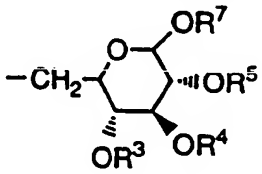
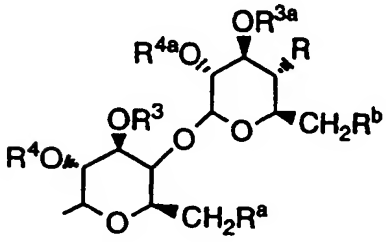


and



; provided that when R^{26} is H or OH, G is not H;

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy or -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl and -C(O)aryl;

R^{30} is independently selected from the group consisting of R^{32}-substitut d T, R^{32}-substituted-T-(C_1-C_6)alkyl, R^{32}-substituted-$(C_2-$

C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C7)cycloalkyl and R^{32}-substituted-(C_3-C7)cycloalkyl(C_1-C_6)alkyl;

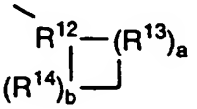
R^{31} is independently selected from the group consisting of H and (C_1-C_4)alkyl;

T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C_1-C_4)alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, (C_1-C_4)alkoxy, methylenedioxy, oxo, (C_1-C_4)alkylsulfanyl, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH(C_1-C_4)alkyl, -C(O)-N((C_1-C_4)alkyl)$_2$, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a (C_1-C_4)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar^1 is aryl or R^{10}-substituted aryl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group  ; and

R^1 is selected from the group consisting of

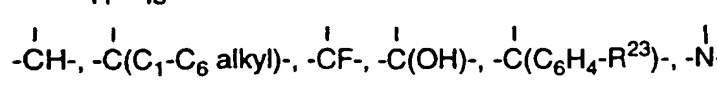
$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e$-E-$(CH_2)_r-$, wherein E is -O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2$-$C_6)$alkenylene-; and

$-(CH_2)_f$-V-$(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R^{12} is



-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C(C_6H_4-R^{23})-, -N-, or $-{}^{+}NO^{-}$;

R^{13} and R^{14} are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(di-(C_1-C_6)$ alkyl), -CH=CH- and $-C(C_1-C_6$ alkyl)=CH-; or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when R^{14} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

and when Q is a bond, R^1 also can be:

$$-M-Y_d-\underset{R^{16}}{\overset{R^{15}}{C}}-Z_h-\ ,\ -X_m-\underset{R^{18}}{\overset{R^{17}}{(C)_s}}-Y_n-\underset{R^{16}}{\overset{R^{15}}{(C)_t}}-Z_p-\ \text{or}\ -X_j-\underset{R^{16}}{\overset{R^{15}}{(C)_v}}-Y_k-S(O)_{0-2}-;$$

M is -O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6)$alkyl- and $-C(di-(C_1-C_6)$alkyl);

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C_1-C_6)alkyl, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1-5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, $-O(CH_2)_{1-10}-COOR^{19}$, $-O(CH_2)_{1-10}CONR^{19}R^{20}$, $-(C_1-C_6$ alkylene)-$COOR^{19}$, $-CH=CH-COOR^{19}$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^{15} and R^{17} are independently selected from the group consisting of $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$ and $-O(CO)NR^{19}R^{20}$; R^{16} and R^{18} are independently selected from the group consisting of H, (C_1-C_6)alkyl and aryl; or R^{15} and R^{16} together are =O, or R^{17} and R^{18} together are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

and when Q is a bond and R^1 is $-X_j-(C)_v-Y_k-S(O)_{0-2}-$ (with R^{15} and R^{16}), Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

R^{21} is (C_1-C_6)alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, (C_1-C_6)alkyl, aryl (C_1-C_6)alkyl, $-C(O)R^{19}$ or $-COOR^{19}$;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -COOH, NO_2, $-NR^{19}R^{20}$, -OH and halogeno; and

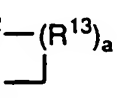
R^{25} is H, -OH or (C_1-C_6)alkoxy.

2. A compound of claim 1 wherein:

Ar^1 is phenyl or halogeo-substituted phenyl;

Ar^2 is phenyl, lower alkoxy-substituted phenyl or halogeno-substituted phenyl;

Q is a bond and R^1 is lower alkylene;

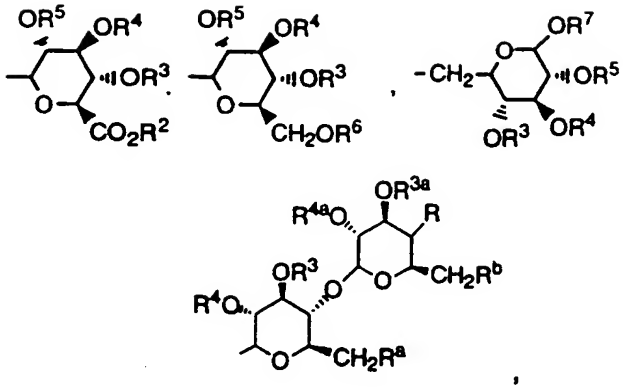
Q, with the 3-position ring carbon of the azetidinone, forms the group  wherein R^{13} and R^{14} are each ethylene and a and b are each 1, and wherein R^{12} is -CH- or -C(OH)- ;

Q is a bond and R^1 is $-O-CH_2-CH(OH)-$;

Q is a bond and R^1 is $-CH(OH)-(CH_2)_2-$; or

Q is a bond and R^1 is $-CH(OH)-CH_2-S(O)_{0-2}-$.

3. A compound of any of claims 1 or 2 wherein G and G^1 are independently selected from the group consisting of H,



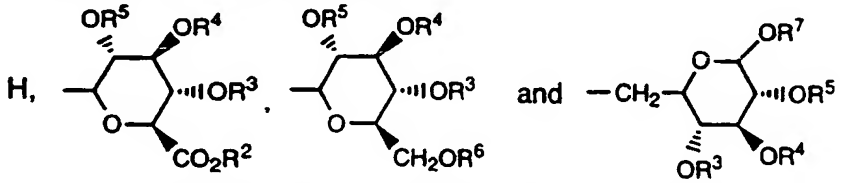
wherein:

R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl;

R^3, R^{3a}, R^4 and R^{4a} are selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl; and

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy and -W-R^{30}, wherein W is -O-C(O)- or -O-C(O)-NR^{31}-, R^{31} is H and R^{30} is (C_1-C_6)alkyl, -C(O)-(C_1-C_4)alkoxy-(C_1-C_6)alkyl, T , T-(C_1-C_6)alkyl, or T or T-(C_1-C_6)alkyl wherein T is substituted by one or two halogeno or (C_1-C_6)alkyl groups.

4. A compound of any of claims 1 to 3 wherein R^{26} is H or OH and G is selected from the group consisting of



wherein R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl.

5. A compound of claim 1 selected from the group consisting of

2,3,4-tri-O-acetyl-1-O-[4-[trans-(3R,4S)-3-[3-[(S)-acetyloxy-3-(4-fluoroph nyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyranuronic acid methyl ester;

1-O-[4-[trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid;

1-O-[4-[trans-(3R,4S)-1-(4-iodophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid;

2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-B-D-gluco-pyranosyl)-1-O-[4-[trans-(3R,4S)-3-[3(S)-acetyloxy-3-(4-fluorophenyl)-propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyran;

1-O-[4-[trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-3-O-(Beta-D-glucpyranosyl)-Beta-D-glucopyranose;

2,3,4,5-tetra-O-acetyl-1-O-[4-[trans-(3R,4S)-3-[3(S)-acetyloxy-3-(4-fluorophenyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyran;

1-O-[4-[trans-(3R,4S)-3-[3(S)-hydroxy-3-(4-fluorophenyl)propyl-1-(4-fluorophenyl)-2-oxo-4-azetidinyl]phenyl]-Beta-D-glucopyranose;

1-O-[4-[trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-fluorophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester;

1-O-[4-[trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenyl)-propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester;

1-O-[4-[trans-(3R,4S)-1-(4-(benzoyl)phenyl)-2-oxo-3-(3-phenyl)-propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid methyl ester;

1-O-[4-[trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenyl-propyl)-4-azetidinyl]phenyl]-Beta-D-glucopyranose;

1-O-[4-[trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenyl-propyl)-4-azetidinyl]phenyl]-Beta-D-glucuronic acid;

1-methyl-6-O-[4-[trans-(3R,4S)-1-(4-methoxyphenyl)-2-oxo-3-(3-phenylpropyl)-4-azetidinyl]phenyl]-Alpha-D-glucopyranoside;

1-O-[4-[trans-(3R,4S)-1-(4-(benzoyl)phenyl)-2-oxo-3-(3-phenyl)propyl]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid; and

1-O-[4-[trans-(3R,4S)-1-(4-fluorophenyl)-2-oxo-3-[3-[(S)-hydroxy-4-iodophenyl)propyl]]-4-azetidinyl]phenyl]-Beta-D-glucuronic acid.

6. A pharmaceutical composition for the treatment or prevention of atherscl rosis, or for the reduction of cholest rol levels, comprising a compound as defined in any of claims 1 to 5, alone or in combination

with a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier.

7. A process for the preparation of a pharmaceutical composition as defined in claim 6 comprising admixing a compound as claimed in any of claims 1 to 5, alone or in combination with a cholesterol biosynthesis inhibitor, with a pharmaceutically acceptable carrier.

8. The use of a compound as claimed in any of claim 1 to 5, alone or in combination with a cholesterol biosynthesis inhibitor, for the manufacture of a medicament for the treatment or prevention of atherosclerosis or for the reduction of cholesterol levels.

9. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat or prevent atherosclerosis or to reduce cholesterol levels which comprises in one container an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier, and in a second container, an effective amount of a compound of any of claims 1 to 5 in a pharmaceutically acceptable carrier.

10. A method of treating or preventing atherosclerosis or reducing cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound claimed in any of claims 1 to 5, alone or in combination with a cholesterol biosynthesis inhibitor, wherein the cholesterol biosynthesis inhibitor, when the combination is administered, can be administered simultaneously or sequentially with the compound of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Intern: nal Application No
PCT/US 96/16823

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H3/04 C07H17/02 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 627 418 A (BRISTOL-MYERS SQUIBB COMPANY) 7 December 1994 see the whole document ---	1
A	JOURNAL OF ORGANIC CHEMISTRY, vol. 59, no. 17, 1994, EASTON US, pages 4714-4716, XP000644310 B.K.BANIK ET AL.: "Stereospecific Glycosylation via Ferrier Rearrangement for Optical Resolution" see abstract ---	1
A	WO 95 08532 A (SCHERING CORPORATION) 30 March 1995 cited in the application see abstract --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1997	05 -03- 1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scott, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 17038 A (SCHERING CORPORATION) 4 August 1994 cited in the application see abstract	1
A	CIRCULATION, vol. 80, no. 5, 1989, pages 1101-1114, XP000617211 J.L.WITZTUM: "Current Approaches to Drug Therapy for the Hypercholesterolemic Patient." cited in the application see the whole document	1
A	DRUGS, vol. 36, no. 3, 1988, pages 63-71, XP000617212 D.R.ILLINGWORTH: "An Overview of Lipid-Lowering Drugs." cited in the application see the whole document	1

6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/16823

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 10 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...mation on patent family members

Internat...l Application No
PCT/US 96/16823

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-627418	07-12-94	US-A-	5412092	02-05-95
		AU-A-	6061194	27-10-94
		CA-A-	2120221	24-10-94
		CN-A-	1097415	18-01-95
		CZ-A-	9400966	15-12-94
		FI-A-	941894	24-10-94
		HU-A-	69373	28-09-95
		JP-A-	7002763	06-01-95
		NO-A,B	941397	24-10-94
		NZ-A-	260322	26-09-95
		ZA-A-	9402069	28-10-94
WO-A-9508532	30-03-95	AU-A-	7795294	10-04-95
		CN-A-	1131416	18-09-96
		CZ-A-	9600839	14-08-96
		EP-A-	0720599	10-07-96
		FI-A-	961300	21-03-96
		HU-A-	73852	30-09-96
		JP-T-	8509989	22-10-96
		NO-A-	961133	20-03-96
		PL-A-	313589	08-07-96
		ZA-A-	9407086	14-03-95
WO-A-9417038	04-08-94	AU-A-	6087294	15-08-94
		CN-A-	1118163	06-03-96
		CZ-A-	9501801	17-01-96
		EP-A-	0681569	15-11-95
		FI-A-	953497	20-07-95
		HU-A-	72592	28-05-96
		JP-T-	8501110	06-02-96
		LT-A,B	1764	27-02-95
		NO-A-	952884	20-09-95
		PL-A-	309978	13-11-95
		SI-A-	9400022	28-02-95
		SK-A-	91195	06-12-95
		ZA-A-	9400386	19-07-94